Anticancer activities of TCM and their active components against tumor metastasis

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ABSTRACT

Traditional Chinese Medicine (TCM) has the characteristics of multiple targets, slight side effects and good therapeutic effects. Good anti-tumor effects are shown by Traditional Chinese Medicine prescription, Chinese patent medicine, single Traditional Chinese Medicine and Traditional Chinese medicine monomer compound. Clinically, TCM prolonged the survival time of patients and improved the life quality of patients, due to less side effects. Cancer metastasis is a complex process involving numerous steps, multiple genes and their products. During the process of tumor metastasis, firstly, cancer cell increases its proliferative capacity by reducing autophagy and apoptosis, and then the cancer cell capacity is stimulated by increasing the ability of tumors to absorb nutrients from the outside through angiogenesis. Both of the two steps can increase tumor migration and invasion. Finally, the purpose of tumor metastasis is achieved. By inhibiting autophagy and apoptosis of tumor cells, angiogenesis and EMT outside the tumor can inhibit the invasion and migration of cancer, and consequently achieve the purpose of inhibiting tumor metastasis. This review explores the research achievements of Traditional Chinese Medicine on breast cancer, lung cancer, hepatic carcinoma, colorectal cancer, gastric cancer and other cancer metastasis in the past five years, summarizes the development direction of TCM on cancer metastasis research in the past five years and makes a prospect for the future.

1. Introduction

Cancer refers to cells in normal tissues of human body that are mutated due to the influence of external factors. The cells lose their original functions and abnormally proliferate to form neoplasms, affecting the normal physiological functions of human body. Cancer has the second highest death rate among all diseases worldwide, only second to cardiovascular and cerebrovascular diseases, and 90 % of cancer deaths are due to metastasis [1,2]. Tumor metastasis represents the process of malignant tumor cells leaving the primary lesion, penetrating through the vessels and entering the host's blood circulation and lymphatic circulation, or directly spreading through the body cavity, reaching the distant site and continuing to proliferate and grow, eventually forming the same type of tumor as the primary lesion [3]. Tumor metastasis is an important indicator of the development of malignancy. Inhibiting tumor metastasis can inhibit tumor cells from metastasizing to other parts of the body, and thus delay tumor deterioration [4].

In the process of tumor metastasis, for cancer cells, the phenomenon of autophagy and apoptosis inhibition will occur, so that the cells acquire more ability of division and proliferation. Autophagy indicates the process in which cytoplasmic proteins or organelles are encapsulated into vesicles of cells, and then form autophagolysosomes with lysosomes and degrade their contents. Moderate autophagy can effectively promote cellular growth, while excessive autophagy will kill cells. Apoptosis is the programmed death of cells. If cells show senescence or abnormality, the cell will start a self-destructive procedure leading to die naturally. The regulatory mechanism in the cancer cell has mutated so that apoptosis cannot occur. Tumor cells accumulate nutrients through angiogenesis, and then undergo epithelial-mesenchymal transition (EMT). Angiogenesis provides tumor cells with sufficient nutrients to accelerate the growth of tumor cells. The blood vessels surrounding the tumor are weaker than the walls of ordinary blood vessels, which allows tumor cells to pass through the wall into the blood and metastasize. Studies have shown that the number of new blood vessels around benign tumors is significantly reduced compared to those of malignant tumors. EMT refers to the process of converting cancer cells from epithelial cells to mesenchymal ones. This makes tumor cells lose some characteristics of epithelial cells, such as intercellular adhesion and cell polarity, and acquire some characteristics of mesenchymal cells, such as movement, invasion, and resistance to apoptosis. EMT changes the type of tumor cells, improves the ability to degrade the matrix, and weakens the intercellular binding force. Therefore, the transformed tumor cells have stronger ability to metastasize and invade, and are more likely to survive in the blood, which is related to drug resistance. EMT makes tumor cells detach from the primary or metastatic foci to form new secondary metastatic foci. Therefore, EMT is considered to be an important process for tumor cells to spread into

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blood circulation [5,6]. Mitochondria also plays an important role in the process of tumor metastasis. Mitochondria can provide energy for cell proliferation, regulate cell metabolism, control the generation of ROS and influence the apoptosis of cancer cells through mitochondrial apoptosis. As a result, mitochondria is involved in many important biological processes in the cell [7]. Hence, in order to inhibit tumor metastasis, autophagy of tumor cells should be increased, and apoptosis of tumor cells should be promoted, therefore the ability of tumor cell division and proliferation can be inhibited. When it comes to tumor, tumor angiogenesis can be reduced and tumor cell EMT should be inhibited. Tumor metastasis can also be suppressed by regulating the function of tumor cell mitochondria.

As the research of tumor mechanism has progressed, many methods have been established to cure cancer, like chemotherapy, radiotherapy, operative treatment, immunotherapy and gene therapy. Chemotherapy and radiotherapy often caused severe side effects. Patients after treatment often show depression, losing appetite, etc. Operative treatment is to excise tumor from the body via clinical surgery, but it limits the minority of cancers. Clinically, immunotherapy and gene therapy have not been popularized. TCM can assist in the treatment of severe side effects caused by radiotherapy and chemotherapy, improve the response rate of radiotherapy and chemotherapy, and improve the life quality of patients [8,9]. In addition, some patients are unable to withstand the side effects of radiotherapy and chemotherapy, so they choose to treat cancer with Chinese herbal compound decoction and get a good therapeutic effect.

In recent years, accumulating evidence of Chinese medicine on cancer metastasis demonstrated the inhibitory effect of TCM prescription on cancer metastasis, the inhibitory effect of Chinese patent medicine on cancer metastasis, the inhibitory effect of single TCM on cancer metastasis, and the molecular mechanism of TCM monomer compound to inhibit cancer metastasis. This review focuses on the recent advances in the treatment of cancer metastasis with TCM. It summarizes the researches of TCM on cancer metastasis in the past five years, mainly including breast cancer which has the highest mortality rate among females, lung cancer which has a high mortality rate, and liver cancer, colorectal cancer and gastric cancer, which are frequent in digestive tract cancers and difficult to diagnose in the early stage (Fig. 1).

2. The advantages of TCM in the treatment of breast cancer

Breast cancer occurs most frequently among women under the age of 40, and is the leading cause of death among women disease with a mortality rate of 23 % [10]. The main causes of breast cancer are external environment stimulation to breast, DNA damage, family inheritance and so on. A large number of studies have shown that breast cancer has a genetic tendency. If the elder women of the family have breast cancer, the chance of the younger women suffering breast cancer will increase greatly. The main reasons for the high mortality rate of breast cancer are the lack of self-awareness, the neglect of breast in clinical examination, and the stimulation of breast by high-fat and low-fiber food [11]. In addition, breast cancer is prone to metastasis, and breast cancer cells themselves can obtain nutrition and oxygen supplied by angiogenesis and then transfer to other new tissues to form secondary tumors, which increases the difficulty of treatment. The overall five-year survival rate for metastatic breast cancer is 27 %, and the prognosis is poor [12,13]. Tumors with a size of more than 5 cm or positive internal breast lymph nodes are more likely to metastasize and the metastatic organs mainly occur in lung, bone, brain, and liver [14,15].

According to pathological process of tumor metastasis, it has been reported that the inhibition of breast cancer metastasis by TCM is through different mechanisms. This review has summarized the reported effective mechanisms of TCM, such as inhibiting EMT, anti- angiogenesis, promoting apoptosis, stimulating autophagy, and suppressing proliferation, migration and invasion of breast cancer cells, shown in Table 1.

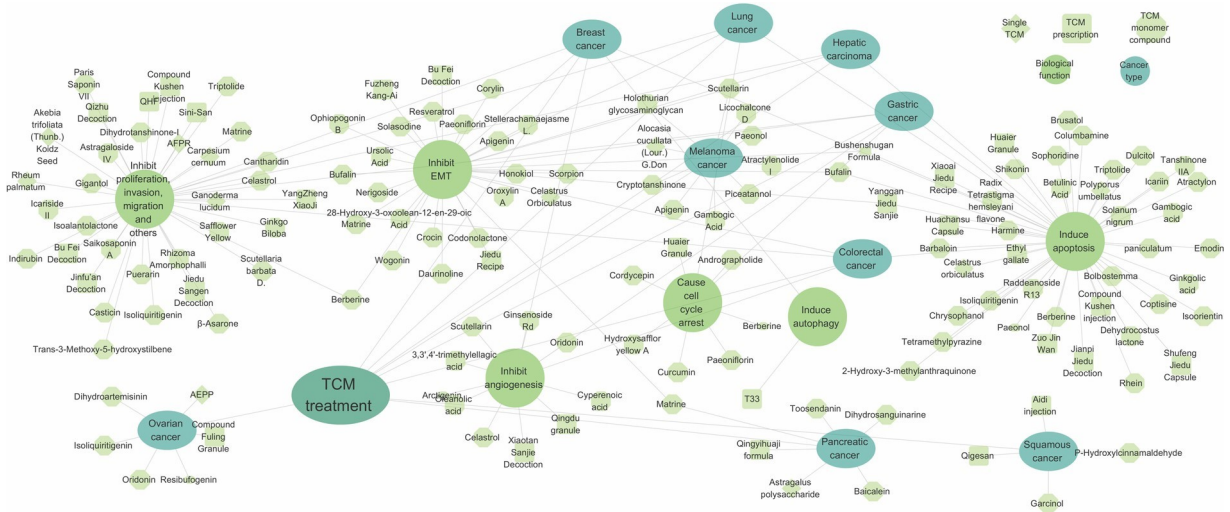

Fig. 1. Network between different TCM treatments and multiple targets of various cancers We used Cytoscape to connect the biological functions of TCM prescription, Chinese patent medicine, single TCM and TCM monomer compound used for cancer. We summarized the potential mechanism of Chinese medicine treatment for different cancers through inhibiting cancer metastasis, including promoting autophagy and apoptosis of cancer cells, and inhibiting EMT and angiogenesis of cancer cells. Diamond represents a single Chinese medicine, Square represents a TCM prescription, Hexagon represents a TCM monomer compound, light green circles represent biological functions, and the light blue circle represents the type of cancer (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 1
The mechanisms of TCM in attenuating breast cancer.

Function	Compound/single TCM	Origin	Molecular mechanism	
Inhibit the EMT	Codonolactone;	*Atractylodes lancea* (Thunb.) DC.	Inhibit phosphorylation of Runx2	[16]
	Oroxylin A;	*Scutellariae radix*	Inhibit NF- κB Signaling Pathway	[17]
	Honokiol;	*Magnolia officinalis* Rehder & E.H. Wilson	Regulates Snail / Slug protein translation	[18]
Inhibit angiogenesis	Arctigenin;	*Arctium lappa* L.	Downregulate MMP-2, MMP-9 and heparanase Inhibit the HIF-1α/VEGF signal pathway; participate in ATP-binding domain of VEGFR2	[24]
	Oridonin;	*Rabdosia rubescens* (Hemsl.) H.Hara.		[20, 21]
	Ginsenoside Rd;	*Panax ginseng* C. A. Mey	Derepressing microRNA-18a-regulated Smad2 express; Regulate Akt/mTOR/p70S6K signaling;	[22, 23]
	Cyperenoic acid	*Croton crassifolius* Geiseler	Attenuating VEGFR2 signal pathway	[25]
Induce apoptosis	*Bolbostemma paniculatum* (Maxim.) Franquet	*Bolbostemma Franquet*	Inhibit mRNA level and protein expression of ARHGAP5	[27]
	Polyporus umbellatus (Pers.) Fries	*Polyporaceae*		[30]
	Betulinic Acid	*Betula mandshurica* (Regel) Nakai	Inhibit AKT expression	[31]
	Tetramethylpyrazine	*Ligusticum striatum* DC.	Regulate GRP78/β-Catenin/c-Myc	[35]
	Harmine	*Peganum harmala* L.	Signaling Inhibit AKT and caspase-3 Target TAZ	[34]
	Ethyl gallate	*Euphorbia fischeriana* Steud.	Inhibit Akt-NF-κB signaling	[36]
	Berberine	*Coptis chinensis* Franch.	Activates caspase-9/cytochrome c-mediated apoptosis	[33]
	Rhein	*Rheum palmatum* L.	Regulate ROS-mediated activation of NF-κB- and p53-signaling pathways	[37]
	Raddeanoside R13	*Pulsatilla chinensis* (Bunge) Regel	Decrease cyclin D1, cyclin A and cyclin E	[38]
Inhibit proliferation, migration, invasion and other function	*Rhizoma Amorphophalli*	*Araceae*	Regulate PI3K/Akt/mTOR pathway; Downregulation KNL1, OLFML2A, RTKN2 and SGO1 gene expression	[41]
	Safflower Yellow	*Carthamus tinctorius* L.		
	Ganoderma lucidum (Reishi)	*Polyporaceae*	Reduces Phosphorylation of Src	[49]
	Active fraction of *Polyrhachis vicina* Rogers (AFPR)	*Formicidae*	Inhibiting Wnt/β-catenin signaling	[42]
	Dihydrotanshinone-I	*Salvia miltiorrhiza* Bunge	Regulating EGR1/lncRNA-NKILA/NF-κB axis Inhibit mRNA expression and post- transcriptional function of HuR	[44]
	Astragaloside IV	*Astragalus propinquus* Schischkin	Inhibits Rac1/MAPK signaling	[45]
	Gigantol	Dendrobium nobile Lindl	Inhibit Wnt/β-catenin signaling	[46]
	Isoalantolactone	*Inula helenium* L.	Regulate p38 MAPK/NF-κB signaling pathway.	[50]
	Saikosaponin A	*Bupleurum chinense* DC.	Downregulate CXCR4	[51]
	Casticin	*Fructus Vitcis Simplicifoliae*	Inhibits PI3K / Akt signaling pathway	[52]
	Puerarin	*Pueraria montana var. lobata* (Willd.) Sanjappa & Pradeep	Inhibit NF-kB and Erk pathway	[53]
	Triptolide	*Tripterygium wilfordii* Hook. f.	Inhibit the expression of miR-146a	[48]
	Isoliquiritigenin	*Glycyrrhiza uralensis* Fisch.	Downregulate miR- 374a	[54]
				[47]

2.1. Inhibiting EMT of breast cancer cells by TCM

Codonolactone, a sesquiterpene lactone, the main component of *Atractylodes lancea* (Thunb.) DC., is reported to be effective in 5-Fluorouracil treated human breast cancer cell MDA-MB-46 CDX (cell line- derived xenografts) model mainly through inhibiting TGF-β1-mediated EMT relative marker in a dose-dependent manner and suppressing phosphorylation of Runx2 [16]. Oroxylin A, a flavonoid isolated from *Scutellariae radix*, inhibits the proliferation and EMT of breast cancer cells through NF-Signaling Pathway [17]. Honokiol a lignans isolated from *Magnolia officinalis* Rehder & E.H.Wilson, has been shown to regulate Snail/Slug protein translation and block EMT [18].

2.2. Blocking the angiogenesis

Qingdu granule, a traditional Chinese herbal prescription, has been validated with five active ingredients: rutin, hesperidin, quercetin, saikosaponins A and saikosaponins D. The

prescription can inhibit the migration and tubule formation of HUVEC cells, down-regulate gene and protein expression and nuclear translocation ratio of NFATc3. In breast cancer cell MCF-7 xenograft model, it inhibits tumor growth, suppresses VEGF release, and reduces the protein expression of VEGF, VEGFR2 and NFATc3 [19].

Oridonin is an active diterpenoid compound isolated from *Rabdosia rubescens* (Hemsl.) H.Hara. On one hand, Oridonin regulates EMT related mRNA and proteins like E-cadherin N-cadhrin and Vimentin, inhibits the migration invasion and adhesion through inhibiting the HIF- 1α/VEGF signal pathway, and suppresses tube formation of HUVECs and microvessel density xenografted by breast cancer 4T1 cells. And on the other hand, Oridonin can enhance the therapeutic effect of doxorubicin through inhibiting the angiogenesis, and reduce myocardial damage caused by the use of doxorubicin [20,21]. Ginsenoside Rd, a saponin isolated from *Panax ginseng* C. A. Mey. can inhibit the tube formation of HUVECs, and it has an inhibitory effect on angiogenesis of breast cancer cells and can promote apoptosis [22,23]. Arctigenin, a lignanolids isolated from *Arctium lappa* L. inhibits the angiogenic capacity through downregulating MMP-2, MMP-9 and heparanase [24]. Cyperenoic acid, a sesquiterpene isolated from *Croton crassifolius* Geiseler inhibits breast cancer metastasis through anti-angiogenesis by attenuating VEGFR2 signal pathway [25].

2.3. Stimulating cell apoptosis

Compound Kushen injection, a common anti-cancer Chinese patent medicine in clinic, can induce the apoptosis of MDA-MB-231 cells and inhibit metastasis. The injection mainly contains eight active ingredients: oxymatrine, oxysophocarpine, nmethylcytisine, matrine, sophocarpine, trifolirhizin, adenine, and sophoridine through LC–MS/ MS analysis. High-throughput sequencing of breast cancer cell MDA- MB-231 treated with Compound Kushen injection total alkaloid reveals that the effect is related to cytoskeleton formation. And experiment has proved that Compound Kushen injection can interrupt F-actin Polymerization, delay the formation of filopodia, inhibit the expansion of lamellipodia, and change the cytoskeleton proteins to inhibit the migration capacity of breast cancer cells [26].

Bolbostemma paniculatum (Maxim.) Franquet, is from *Bolbostemma* Franquet, whose total extract can inhibit the proliferation and metastasis of breast cancer cells, inhibit the lung metastasis in animals, and reduce the mRNA level and protein expression of ARHGAP5. Total saponins of *Bolbostemma paniculatum* (Maxim.) Franquet can induce breast cancer cell apoptosis and inhibit its metastasis by inhibiting the PI3K/ Akt/mTOR pathway [27,28]. *Solanum nigrum* L. from *Solanum* L. can suppress mitochondrial function, cause apoptosis, and then inhibit EMT of breast cancer cells [29]. *Polyporus umbellatus* (Pers.) Fries, belonging to Polyporaceae, promotes apoptosis by down-regulating AKT expression [30].

Betulinic Acid, a pentacyclic triterpenes extract from *Betula mandshurica* (Regel) Nakai, induces GRP78 overexpression, suppresses the β-Catenin-Mediated Aerobic Glycolysis in vitro and inhibits lung metastasis of breast cancer by GRP78/β-Catenin/c-Myc Signaling in vivo [31]. Tetramethylpyrazine from *Ligusticum striatum* DC., Harmine extracted from *Peganum harmala* L. and Berberine extracted from *Coptis chinensis* Franch., and all of the three alkaloids have been proved to be effective in inducing apoptosis [32–35]. Ethyl gallate, a diterpenoids isolated from *Euphorbia fischeriana* Steud., inhibits Akt-NF-κB signaling pathway and induces apoptosis [36]. Rhein, an anthraquinone extracted from *Rheum palmatum* L., induces apoptosis, and causes cell cycle arrest in breast cancer [37]. Raddeanoside R13, a saponin isolated from *Pulsatilla chinensis* (Bunge) Regel promotes autophagy and apoptosis via regulating related makers [38].

2.4. Inducing cell autophagy

Chinese medicine formula T33, based on TCM prescription Gan Sui Ban Xia Tang, is composed of *Radix Kansui, Paeonia lactiflora, Pinelliae Rhizoma Praeparatum*, *Glycyrrhizae Radix et Rhizoma*, and *Rheum rhabarbarum*. Clinically, it is often used for patients with hidden pulse, spontaneous diarrhea and malignant pleural effusion. Experiment has found that T33 can induce autophagy to inhibit the growth and invasion of MDA-MB231 and MCF-7 cells of breast cancer, without significant inhibition on normal human mammary epithelial cells HMEpiC cells. It also has an inhibitory effect on tumor xenografts of MDA-MB-231 and MCF-7 cells [39].

2.5. Suppressing proliferation, migration and invasion of breast cancer cells by TCM

Rhizoma Amorphophalli from Araceae inhibits the proliferation, invasion, and metastasis of MDA-MB-231 cells through the PI3K/Akt/ mTOR pathway. And it downregulates the KNL1, OLFML2A, RTKN2 and SGO1 gene expression, which can induce cell cycle arrest and inhibit the invasion of xenograft tumors in tail vein injection in animals [40,41]. *Ganoderma lucidum* (Reishi) from Polyporaceae can suppress proliferation and migration of breast cancer cells through inhibiting Wnt/β-catenin signaling pathway [42]. *Carpesium cernuum* L. from Compositae was given to breast cancer cells, and genome-wide transcriptome analysis revealed that the gene expression affected by *Carpesium cernuum* L. extract was mainly related to metastasis [43]. The active fraction of *Polyrhachis vicina* Rogers (AFPR) can inhibit breast cancer migration through regulating EGR1/lncRNA-NKILA/NF-κB axis [44].

Dihydrotanshinone-I, a phenanthraquinones isolated from *Salvia miltiorrhiza* Bunge, inhibits the mRNA expression and post- transcriptional function of HuR to inhibit breast cancer metastasis [45]. Astragaloside IV, a saponin isolated from *Astragalus propinquus* Schischkin, inhibits Rac1/MAPK signaling regulated by Vav3 to inhibit the invasion ability of breast cancer cells [45]. Flavonoids compounds, Safflower Yellow from *Carthamus tinctorius* L.

inhibits lung metastasis of breast cancer by inhibiting invadopodia formation and reduces Phosphorylation of Src. Puerarin from *Pueraria montana var. lobata* (Willd.) Sanjappa & Pradeep inhibits the invasion and migration of breast cancer cells by inhibiting the NF-κB and Erk pathway [46]. Isoliquiritigenin from *Glycyrrhiza uralensis* Fisch. suppresses breast cancer metastasis through downregulating miR- 374a [47–49]. Gigantol, a hydroxybenzene isolated from *Dendrobium nobile* Lindl. exhibits anticancer activity in breast cancer cells through Wnt/β-catenin signaling pathway [50]. Isoalantolactone, a sesquiterpene lactone isolated from *Inula helenium* L. inhibits the metastasis of breast cancer through p38 MAPK/NF-κB signaling pathway [51]. Saikosaponin A, a triterpenoid glycoside isolated from *Bupleurum chinense* DC. inhibits the proliferation and metastasis of breast cancer in breast cancer cell and animal xenograftmodels [52]. Casticin, a polymethoxyflavone isolated from *Fructus Vitcis Simplicifoliae* inhibits PI3K / Akt signaling pathway and inhibits breast cancer cell metastasis [53]. Triptolide, an epoxy diterpene lactone isolated from *Tripterygium wilfordii* Hook. f. suppresses the metastasis of breast cancer cell through inhibiting the expression of miR-146a [54].

In the study of TCM treating breast cancer metastasis, compound Kushen injection is a commonly used anti-tumor drug in clinic and the main components are also clear. In the research on the role of breast cancer, the genes found by sequencing and their classifications make the whole experiment more accurate and reliable. Clinically, precise medication will be more meaningful. For clinical patients, we can first determine whether the drug has specific therapeutic effects by detecting the gene expression of patient tumor. When it comes to the clinical application of TCM, an important point is to reduce the toxicity and side effects of chemotherapy drugs and to enhance the efficacy of chemotherapy drugs. Oridonin has effect in reducing doxorubicin induced side effect and toxicity to body. Different drugs inhibit breast cancer metastasis through different molecular mechanisms or modes of action. **3. The advantages of TCM in the treatment of lung cancer**

Lung cancer has the highest mortality rate among all cancers [55]. Lung cancer can be divided into small cell lung cancer and non-small cell lung cancer, and the ratio of non-small cell lung cancer is as high as 80 % [56]. There are many causes of lung cancer, including smoking, working conditions, ionizing radiation and past lung infections. The cause of death of most lung cancer patients is the metastasis of lung cancer [57]. Lung cancer cells escape the recognition of the immune system through EMT mutation and can easily enter the circulatory system including blood vessels and lymphatic vessels and then enter the brain, bone and adrenal glands which are prone to metastases in the early stage [58]. Brain is the most easily metastasized organ in lung cancer, and its metastasis rate is as high as 50 %. Brain metastasis has a high metastasis rate and is difficult to control. One of the main reasons lies in the blood-brain barrier. Many drugs are difficult to cross the blood-brain barrier, and that is why the treatment of lung cancer is inefficient [59].

According to pathological process of tumor metastasis, it has been reported that lung cancer metastasis can be inhibited by TCM through different mechanisms. This review has summarized the reported effective mechanisms of TCM, such as inhibiting EMT, promoting apoptosis, causing cell cycle arrest, and suppressing proliferation, migration and invasion of breast cancer cells, shown in Table 2.

3.1. Inhibiting EMT of lung cancer cells by TCM

Bu-fei Decoction is a TCM prescription, which is commonly used clinically for patients with lung Qi deficiency. Xi-Ran He et al. have found that Bufei Decoction can inhibit the metastasis and invasion of lung cancer by inhibiting the EMT-related protein marker of lung cancer cells induced by TGF-β1, and this function is achieved by reducing the expression of canonical Smad signaling pathway [60]. Fuzheng Kang-Ai decoction suppresses EMT though regulating the STAT3/MMP9 pathway [61]. Bushenshugan Formula regulates EMT-related markers through PI3K/AKT/NF-κB pathway [62].

Ophiopogonin B, a saponin extracted from *Ophiopogon japonicus* (Thunb.) Ker Gawl., can suppress EMT through EphA2/Akt signaling

Table 2
The mechanisms of TCM in attenuating lung cancer.

Function	Compound/single TCM	Origin	Molecular mechanism	
Inhibit the EMT	Ophiopogonin B	*Ophiopogon japonicus* (Thunb.) Ker Gawl.	Regulate EphA2/Akt signaling pathway and Linc00668/miR-432− 5p/EMT	[63]
	Bufalin	*Bufo bufo gargarizans* Cantor	Suppress TGF-β receptor	[64]
	Wogonin	*Scutellaria baicalensis* Georgi	Regulate IL-6/STAT3 signaling pathway	[65]
	Matrine	*Sophora flavescens* Aiton	Inhibit PAX2	[66]
Induce apoptosis	Chrysophanol	*Rheum palmatum* L.	Suppress HIF-1a/VEGF	[69]
	Barbaloin	*Aloe barnadensis*	Inactive p38MAPK/Cdc25B/Hsp27 pathway	[70]
	2-Hydroxy-3-methylanthraquinone	*Hedyotis diffusa*	Regulate JAK2/STAT3 pathway	[71]
Cause cell cycle arrest	Cordycepin	*Cordyceps Sinensis*	Activate AMPK pathway	[72]
	Hydroxysafflor yellow A	*Carthamus tinctorius* L.	Inhibit PI3K/AKT/mTOR and ERK/MAPK signaling pathways	[73]
	Curcumin	*Curcuma longa* L.	Inhibit TLR4/MyD88 and EGFR	[74]
Inhibit proliferation, invasion, migration and other function	Triptolide	*Tripterygium wilfordii* Hook. f.	Inhibit FAK Protein expression	[79]
	Paris Saponin VII	*Trillium tschonoskii* Maxim.	Downregulate the expression of TIMP-1/2 and E-cadherin	[80]
	Icariside II	*Epimedium koreanum* Naka	Downregulate Akt/NF-kB Signaling Pathway	[81]
	Trans-3-Methoxy-5-hydroxystilbene	*Alpinia nantoensis* F.Y.Lu & Y. W.Kuo	Downregulate MMPs and β-catenin	[82]
	β-Asarone	*Acorus calamus* L.	Suppress Wnt/β-catenin signaling	[83]

pathway and Linc00668/miR-432-5p/EMT Axis [63]. Bufalin, a steroid extract from *Bufo bufo gargarizans* Cantor, inhibits TGF-β induced EMT through suppressing TGF-β receptor [64]. Wogonin, a flavonoid extracted from *Scutellaria baicalensis* Georgi, inhibits EMT induced by inflammatory microenvironment through IL-6/STAT3 signaling pathway [65]. Matrine, an alkaloid extracted from *Sophora flavescens* Aiton, downregulates the PAX2 induced EMT marker to suppress migration of lung cancer [66].

3.2. Stimulating cell apoptosis

Bushenshugan Formula and Huaier Granule extract has functioned in inducing apoptosis [62,67]. Xiaoai Jiedu Recipe induces apoptosis through activating P38 MAPK pathway in lung cancer cell line A549 cells [68].

Anthraquinone, a Chrysophanol from *Rheum palmatum* L. induces apoptosis of lung cancer through accumulating the ROS, inhibits angiogenesis by inhibiting the tube formation of HUVECs, and suppresses expression of HIF-1a/VEGF. As a result, Chrysophanol inhibits the migration of lung cancer cells especially in high vascularized tumors. Barbaloin from *Aloe barnadensis* exerts antimetastasis effect through inducing apoptosis of lung cancer by inactivating p38MAPK/Cdc25B/Hsp27 pathway. 2-Hydroxy-3-methylanthraquinone, from *Hedyotis diffusa* induces apoptosis through IL-6-induced JAK2/STAT3 pathway [69,71].

3.3. Causing cell cycle arrest

Huaier Granule extract causes cell cycle arrest in the G0 / G1 phase through inhibiting MTDH, JAK2/STAT3 and MAPK signaling pathways [67].

Cordycepin, a nucleosides isolated from *Cordyceps Sinensis*, weakens the migration and invasion of lung cancer cells, and the mechanism is

associated with inhibition of S and G2 / M phase and induces apoptosis. It shows that it is achieved by activating the AMPK pathway, and the same conclusion has been obtained in in vivo [72]. Hydroxysafflor yellow A, a flavonoid isolated from *Carthamus tinctorius* L., suppresses the PI3K/AKT/mTOR and ERK/MAPK signaling pathways, and induces apoptosis of lung cancer [73]. Curcumin, a diketones isolated from *Curcuma longa* L. inhibits TLR4/MyD88 and EGFR and induces G2/M phase cell cycle arrest in NSCLC cell lines [74]. Paeoniflorin, a pinane monoterpene bitter glycosides extracted from *Paeonia lactiflora* Pall., suppresses metastasis of lung cancer through inducing cell cycle arrest [75].

3.4. Suppressing proliferation, migration and invasion of lung cancer cells by TCM

Jinfu'an Decoction down-regulates p120ctn, and up-regulates the expression of Kaiso [76]. YangZheng XiaoJi inhibits the metastasis of lung cancer induced by HGF to inhibit the growth of lung cancer [77]. Bu Fei Decoction has functioned in regulating IL-10 and PD-L1 to inhibit proliferation, invasion and migration [78].

Triptolide is an epoxy diterpene lactone extracted from *Tripterygium wilfordii* Hook. f. Through RNA sequencing of lung cancer cells after Triptolide administration, it is found that Triptolide can inhibit the expression of lung cancer cell metastasis-related mRNA. Experiments have verified that it indeed inhibited the migration of lung cancer cells, and the inhibition of metastasis was achieved through the inhibition of FAK Protein expression. in vivo, by injecting lung cancer cells into the tail vein of NSG mice, it was found that the lung tumors of mice were reduced, which confirmed the inhibition of breast cancer cell metastasis [79]. Paris Saponin VII, a saponin extracted from *Trillium tschonoskii* Maxim., downregulates the expression of TIMP-1/2 and E-cadherin in inhibiting human lung cancer A549 metastasis [80]. Icariside II, a flavonol glycosides extracted from *Epimedium koreanum* Nakai, inhibits migration via downregulating Akt/NF-kB signaling pathway [81]. Trans-3-Methoxy-5-hydroxystilbene, a stilbene from *Alpinia nantoensis* F.Y.Lu & Y.W.Kuo, also can inhibit metastasis [82]. β-Asarone, from *Acorus calamus* L., inhibits lung cancer invasion and migration through suppressing Wnt/β-catenin signaling pathway [83].

We have investigated the TCM treatment for lung cancer metastasis. TCM prescription, Fuzheng Kang-Ai decoction, has been used to treat patients with NSCLC at Guangdong Provincial Hospital of TCM and has a positive effect. Jinfu'an Decoction has been used for lung cancer patients in Guangzhou University of Chinese Medicine and shows mitigation of clinical symptoms and signs. YangZheng XiaoJi also has good effect in patient with lung cancer. Surprisingly, Ophiopogonin B has functioned in regulating Linc00668/miR-432-5p/EMT Axis, through regulating lincRNA and miRNA, prompting a new way for TCM in treatment of cancer besides lung cancer. Chemical components in Chinese medicine Chrysophanol has been found to have multiple functions in inducing apoptosis, antiangiogenesis, and inhibiting proliferation, invasion and migration of lung cancer involved in every stage of cancer cell metastasis.

4. The advantages of TCM in the treatment of hepatic carcinoma

Among all cancers, the death rate of liver cancer ranks second, only second to lung cancer, and the death rate of liver cancer ranks first among digestive tract cancers. Liver cancer is a malignant tumor that occurs in the liver and can be divided into two types: primary liver cancer and secondary hepatocellular carcinoma. Primary liver cancer refers to a malignant tumor that originally occurred in the epithelial tissue of the liver, and its inducement includes two aspects of diet and the external environment [84]. Excessive drinking can induce alcoholic liver and then develop into liver cancer. Excessive fat intake and obesity in the diet can cause fatty liver and then liver cancer. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the least likely causes of liver cancer. People with hepatitis B and C viruses can pass the virus on to others because of the lack of medical knowledge. These two viruses can cause hepatitis, which develops into cirrhosis and then liver cancer. Aflatoxin, nitrosamine and other substances with strong hepatotoxicity are also the main cause of liver cancer [85]. Secondary hepatocellular carcinoma (HCC) is a cancer that occurs when other malignancies such as colorectal cancer, stomach cancer, lung cancer, breast cancer, and pancreatic cancer metastasized to the interlobular tissues of the liver [84]. The metastasis rate of liver cancer is high often

related to intrahepatic, gallbladder and lung. Due to the large surface area and volume of the liver, if liver cancer cells are to metastasize, they first occur inside the liver. Gallbladder is closer to the liver and becomes the first metastasis of liver cancer. Liver is the main organ that produces blood. Hematogenous metastasis can occur, and the range of hematogenous metastasis is wider than the whole body. Therefore, if liver cancer metastasizes, it will cause greater difficulties for its treatment.

According to pathological process of tumor metastasis, it has been reported that the inhibition of hepatic cancer metastasis by TCM are through different mechanisms. This review has summarized the reported effective mechanisms of TCM, such as inhibiting EMT, promoting apoptosis, and suppressing proliferation, migration and invasion of hepatic cancer cells, shown in Table 3.

4.1. Inhibiting EMT of hepatic cancer cells by TCM

TCM prescription Jiedu Recipe including *Actinidia valvata* Dunn, *Salvia chinensis* Benth., *Cremastra appendiculata* (D.Don) Makino and *Gallusgallusdomesticus* Brisson, have been used clinically for the treatment of liver cancer for decades. Shufang Liang et al. found that its effect on liver cancer is to inhibit the EMT of liver cancer cells induced by TGF- β1 and inhibit the metastasis and invasion of liver cancer cells. The mechanism is actually through regulating the Smad-related pathways or regulating the MAPKs and Akt-related pathways [86]. Yanggan Jiedu Sanjie inhibits TGF-β1-induced EMT [87,88].

The extract of *Celastrus orbiculatus* Thunb. from Celastraceae and Scorpion has been investigated to inhibit EMT of Human Hepatocellular Carcinoma. *Celastrus orbiculatus* Thunb. is through regulating the Hif- 1α/ Twist1 signal pathway [89,90]. Extract of *Stellera chamaejasme* L. from Thymelaeaceae. inhibits proliferation and EMT related maker of Hepatocellular Carcinoma. Through analysis of miRNA expression, hsa-miR-107 and hsa-miR-638 are upregulated after treated with extract of *Stellera chamaejasme* L. [91].

Matrine, an alkaloid and the main extract of *Sophora flavescens* Aiton, regulates EMT related protein, decreases the Vimentin expression and increases E-cadherin expression. In order to explore its more accurate target, molecular docking and SPR are used to explore EMT-related proteins. Finally Matrine can bind into the protein of MMP9 suppressing its activity, and as a result Matrine can inhibit lung metastasis of hepatocellular carcinoma [92,94]. Flavonoids, a Corylin from *Cullen corylifolium* (L.) Medik., inhibits Long Noncoding RNA GAS5 mediated EMT and finally influences progression of hepatocellular carcinoma. Scutellarin from *Scutellaria baicalensis* Georgi can remode the cytoskeleton of hepatocellular carcinoma, and inhibit EMT through JAK2/STAT3 signaling pathway [95,96]. Bufalin, a steroid isolated from *Bufo bufo gargarizans* Cantor, inhibits EMT of liver cancer through Wnt/β-catenin signaling pathway [97].

4.2. Inducing cell apoptosis

TCM formulation Yanggan Jiedu Sanjie induces apoptosis, activates caspase activity in human

Table 3
The mechanisms of TCM in attenuating hepatic cancer.

Function	Compound/single TCM	Origin	Molecular mechanism	
Inhibit EMT	*Celastrus orbiculatus* Thunb.	*Celastraceae*	Hif-1α/ Twist1 signal pathway	[89]
	Stellera chamaejasme L.	*Thymelaeaceae* Juss.	Up regulate hsa-miR-107 and hsa-miR-638	[91]
	Matrine	*Sophora flavescens* Aiton	Binding to protein of MMP9	[92,93,94]
	Corylin	*Cullen corylifolium* (L.) Medik.	Inhibit Long Noncoding RNA GAS5	[95]
	Scutellarin	*Scutellaria baicalensis* Georgi	Regulate JAK2/STAT3 signal pathway	[96]
	Bufalin	*Bufo bufo gargarizans* Cantor	Inhibit Wnt/β-catenin signaling pathway	[97]
Induce apoptosis	Isoorientin	*Gypsophila elegans* M.Bieb.	Regulate mitochondrial related gene expression	[99]
	Atractylon	*Atractylodes lancea* (Thunb.) DC. and *Atractylodes chinensis* (DC.) Koidz.		[100]
	Coptisine	*Coptis chinensis* Franch.	Downregulate MMP-2 and MMP-9 expression	[101]
	Dulcitol	*Euonymus alatus* (Thunb.) Siebold		[102]
	Rhein	*Rheum palmatum* L.	Up-regulate miR-122 Regulate SIRT1/p53 pathway	[103,104]
	Brusatol	*Brucea javanica* (Linn.) Merr.	Regulate MPT Up regulate FOXO3-mediated Bim Regulate PI3K/Akt/mTOR pathway	[105]
	Columbamine	*Coptis chinensis* Franch.	Down-regulation of PI3K/AKT, p38 and ERK1/ 2 MAPK signaling pathways	[106]
	Emodin	*Rheum palmatum* L.	Activate the p38 MAPK signaling pathway; Suppress the ERK/MAPK and PI3K/Akt signaling pathways	[107]
	Bufalin	*Bufo bufo gargarizans* Cantor	Suppress poly (I: C)	[108]
Inhibit proliferation, migration, invasion and other function.	*Akebia trifoliata* (Thunb.) Koidz.	*Lardizabalaceae* R. Br.	Regulate FAK adhesion signaling, cadherin molecules and MMPs	[113]
	Rheum palmatum L.	*Polygonaceae*	Regulate STAT3	[114]
	Indirubin	*Indigofera tinctoria* L.	Inhibit angiogenesis.	[115]

hepatocarcinoma Bel-7402 cells [87]. Shufeng Jiedu Capsule promotes the treatment effect of doxorubicin and can induce apoptosis and suppress invasion and migration of hepatocellular carcinoma [98].

Isoorientin, a flavonoid glycoside from *Gypsophila elegans* M.Bieb., has functioned in causing cell cycle arrest at G1 phase by regulating cell-cycle related genes and ROS accumulation. Finally, these functions are attributed to inducing apoptosis of hepatic cancer cell through mitochondrial-mediated pathway [99]. Atractylon, a sesquiterpenoid isolated from *Atractylodes lancea* (Thunb.) DC. and *Atractylodes chinensis* (DC.) Koidz., reduces mitochondrial membrane potential, induces apoptosis, increases ROS, suppresses EMT, and inhibits invasion and migration of hepatocellular carcinoma in vivo and in vitro [100]. Coptisine, an alkaloid extracted from *Coptis chinensis* Franch., can up-regulate miR-122, the direct target involved in cell proliferation, migration, differentiation and apoptosis, and suppress the hepatocellular carcinoma [101]. Dulcitol from *Euonymus alatus* (Thunb.) Siebold regulates SIRT1/p53 pathway, induces apoptosis and suppresses invasion of hepatocellular carcinoma [102]. Rhein, an anthraquinone isolated from *Rheum palmatum* L. causes cell cycle arrest, and induces mitochondrial dysfunction and apoptosis of hepatocellular carcinoma [103,104]. Brusatol, a quassinoid isolated from *Brucea javanica* (Linn.) Merr., can cause apoptosis and autophagy via the PI3K/Akt/mTOR pathway, hence inhibiting migration of hepatocellular carcinoma [105]. Columbamine, an alkaloid isolated from *Coptis chinensis* Franch., suppresses PI3K/AKT, p38 and ERK1/2 MAPK signaling pathway and induces apoptosis, hence inhibiting hepatocellular carcinoma [106]. Emodin, an anthraquinone extracted from *Rheum palmatum* L., induces apoptosis and inhibits metastasis by activating the p38 MAPK signaling pathway and suppressing the ERK/MAPK and PI3K/Akt signaling pathways [107]. Bufalin induces apoptosis and suppresses poly (I: C)-inspired Hepatocellular Carcinoma metastasis [108].

4.3. Suppressing proliferation, migration and invasion of liver cancer cells by TCM

Chinese medicine Sini-San consists of Chaihu (*Radix Bupleuri Chinensis*), Baishao(*Radix Paeoniae Alba*), Zhishi (*Fructus Aurantii Immaturus*), and Gancao (*Radix Glycyrrhizae*), proportioned at a ratio of 1:1:1:1 and clinically used in treating liver injury. Experimentally, Sini-San can inhibit hepatitis B X-protein induced migration and invasion of human hepatocellular carcinoma cells via downregulating PI3K/AKT and decreasing and inhibiting MAPK and IκB pathway signaling [109]. Li Gao et al. have investigated Compound Kushen Injection, which has an effect on inhibiting hepatocellular carcinoma. Using UPLC-MS analysis, it was found that Kushen Injection contains 22 main components and five main components are matrine, oxymatrine, sophoridine, N-methylcytisine and oxysophocarpine. And then the inhibition mechanism of the injection was mapped a network to predict targets [110]. Chinese herbal formula QHF (Q, Qingrejiedu; H, Huoxuehuayu; and F, Fuzhengguben) suppresses migration and invasion of hepatocellular carcinoma through inhibiting ERK, p38 and JNK [111]. Extracts of Qizhu decoction suppresses hepatocellular carcinoma through multiple functions including inhibiting EMT, inducing cell cycle arrest, and inducing apoptosis in vivo and in vitro via NF-κB signaling pathway [112].

Akebia trifoliata (Thunb.) Koidz. is from Lardizabalaceae, and the extract has been investigated to inhibit migration of Hepatocellular Carcinoma but having no effect on apoptosis [113]. *Rheum palmatum* L. extract, from Polygonaceae, has an effect on STAT3, inhibiting invasion, migration and has function in inhibiting angiogenesis of HUVECs [114]. Indirubin, a bisindole alkaloid extracted from *Indigofera tinctoria* L., inhibits angiogenesis by suppressing HUVEC cells, and finally inhibits migration and invasion [115].

Reviewing the research of Chinese medicine on liver cancer metastasis in recent five years, Jiedu Recipe has been used for hepatic carcinoma patient for many years [116]. Compound Kushen Injection (CKI) was approved by the State Food and Drug Administration of China 15 years ago. The composition of CKI and its possible targets were examined by a CKI target aggregation network. We think that it may give us a method to investigate the mechanism of TCM prescription and Chinese patent medicine. We have found that many TCM have functioned in regulating mitochondria to induce apoptosis, such as Rhein inducing mitochondrial dysfunction, Isoorientin activating mitochondrial-mediated pathway and Atractylon reducing mitochondrial membrane potential.

5. The advantages of TCM in the treatment of colorectal cancer

Colorectal cancer is a cancer caused by abnormal proliferation of colon and rectal cells. The causes of colorectal cancer have not been determined, but generally include irregular diet, genetic mutations and family inheritance. A diet low in fiber and high in fat has significantly increased the risk of colorectal cancer in modern people. Colorectal cancer is more common in people over the age of 40. In early years, colorectal cancer was more common in men. In recent years, the prevalence among women has shown an upward trend. Early colon cancer early manifests as mild blood in the stool, which makes diagnosis of colon cancer difficult. And intestinal diseases such as hemorrhoids also appear as mild blood in the stool. In the later stage of colon cancer, patients with symptoms of anemia are caused by frequent blood in the stool, and patients are debilitated and have general weakness due to chronic malnutrition. Colorectal cancer cell migrate to other tissues and organs through lymphatic and blood circulation. Direct spread mainly include liver, lung and gastric and those with liver as the primary metastasis account for 30–60 % and the five-year survival rate after metastasis is only 20 % [117,118].

According to the pathological process of colorectal cancer metastasis, it has been reported that colorectal cancer metastasis is inhibited by TCM

through different mechanisms. This review has summarized the reported effective mechanisms of TCM, such as inhibiting the EMT, promoting apoptosis, inhibiting angiogenesis and inhibiting the proliferation, migration, invasion and other functions, shown in Table 4.

5.1. Inhibiting EMT of colorectal cancer cells by TCM

Resveratrol is a non-flavonoid polyphenol extracted from *Veratrum grandiflorum* (Maxim. ex Miq.) O.Loes., served as EMT inhibitor. Qing Ji et al. found that Resveratrol could inhibit cell metastasis in mice injected with colorectal cancer cells through the tail vein, and could also inhibit the metastasis of orthotopic colon tumors in mice. Further research on its cell function found that Resveratrol could inhibit TGF- β1-induced EMT through Smads signaling pathway. Li Yuan et al. found that Resveratrol inhibited EMT through the AKT/GSK3β/Snail signaling pathway [119,120]. Nerigoside, a cardenolide isolated from *Nerium oleander* L., inhibits migration of colorectal cancer cell through inhibiting EMT and causing cell cycle arrest on G2/M, and suppressing ERK/GSK3β/β-catenin signaling pathway [121]. Apigenin, Berberine and Paeoniflorin function as an inhibitor of EMT to colon cancer migration through different signaling pathway [122–124]. Solasodine, an alkaloid isolated from *Solanum nigrum* L. can inhibit stemness and EMT of colon cancer in vitro and vivo [125]. Ursolic Acid, a pentacyclic triterpenes isolated from *Hedyotic diffusa*/*Scutellaria barbata*/*Spica prunellae*/*Patrinia scabiosaefolia*, suppresses EMT and potential invasion of colorectal cancer cells via TGF-β1/ZEB1/miR-200c signaling pathway [126].

5.2. Inducing cell apoptosis

Jianpi Jiedu decoction is clinically used in combination with other drugs to treat colorectal cancer, and can improve the prognosis of patients. The molecular mechanism has been found that Jianpi Jiedu decoction induces apoptosis and inhibits invasion of colorectal cancer through mTOR/HIF-1α/VEGF pathway [127,128]. Extracts of Zuo Jin Wan contains two Chinese herb: Rhizoma Coptidis and Evodia rutaecarpa with a ratio of 6:1, which is clinically commonly used to treat the liver-fire. It causes cell cycle arrest in G1 and induces apoptosis through inactivating Wnt/β-catenin signaling pathway [129].

Tanshinone IIA, a phenanthraquinone as a good medicinal effect extract, can cause mitochondrial fission by activating JNK-Mff signaling pathway, induce apoptosis, and inhibit proliferation and migration in colon cancer cell [130,131]. Triptolide, an epoxy diterpene lactone from *Tripterygium wilfordii* Hook. f., suppresses migration and invasion of colorectal cancer through downregulating the expression of miR-191, induces apoptosis and inhibits EMT [132,133]. Sophoridine from *Sophora flavescens* Aiton, can induce apoptotic and autophagy through inactivating MAPKAPK2, and suppress migration of colon cancer. Coptisine, from *Coptis chinensis* Franch., induces mitochondrial-mediated apoptotic, and inhibits invasion of colon cancer in vivo and in vitro. Columbamine, from *Coptis chinensis* Franch. can induce apoptosis and inhibit proliferation and invasion of colon cancer through Wnt/β-catenin signaling pathway [134–136]. Dehydrocostus lactone, a sesquiterpene lactone extracted from *Aucklandia lappa* DC., can induce cell cycle arrest in the G0/G1 phase, cause cell

Table 4
The mechanisms of TCM in attenuating colon cancer.

Function	Compound/single TCM	Origin	Molecular mechanism	
Inhibit the EMT	Resveratrol	*Veratrum grandiflorum* (Maxim. ex Miq.) O. Loes.	Inhibits Smads signaling pathway Inhibit AKT/GSK-3β/Snail signaling pathway	[119, 120]
	Nerigoside	*Nerium oleander* L.	Suppress ERK/GSK3β/β-catenin signaling pathway	[121]
	Apigenin	*Plantago asiatica* L. or *Plantago depressa* Willd.	Regulate NF-κB/Snail signaling pathway	[122]
	Berberine	*Coptis chinensis* Franch.	Regulate TGF-β pathway	[123]
	Solasodine	*Solanum nigrum* L.	Inhibit TGF-β1	[125]
	Ursolic Acid	*Hedyotic diffusa*/*Scutellaria barbata*/ *Spica prunellae*/ *Patrinia scabiosaefolia*	Regulate TGF-β1/ZEB1/miR-200c signaling pathway	[126]
Induce apoptosis	Tanshinone IIA	*Salvia miltiorrhiza* Bunge	Activate JNK-Mff signaling pathway	[130, 131]
	Triptolide	*Tripterygium wilfordii* Hook. f.	Downregulate miR-191	[132, 133]
	Sophoridine	*Sophora flavescens* Aiton	Inactive MAPKAPK2	[134]
	Dehydrocostus lactone	*Aucklandia lappa* DC.	downregulate of eIF4E expression	[137]
	Coptisine	*Coptis chinensis* Franch.	Regulate PI3K/Akt	[135]
	Ginkgolic acid	*Ginkgo biloba* L.	Reduce mTORC1	[138]
	Gambogic acid	*Garcinia hanburyi* Hook.f.	Regulate PI3K/AKT/P21 signaling and MMP-2 and -9 activity	[139]
	Icariin	*Epimedium brevicornu* Maxim.	Regulate P53	[140]
	Columbamine	*Coptis chinensis* Franch.	Regulate Wnt/β-catenin signaling pathway	[136]
	Shikonin	*Lithospermum erythrorhizon* Siebold & Zucc.	Regulate galectin-1/JNK signaling	[142]
	Radix Tetrastigma hemsleyani flavone	*Tetrastigma hemsleyanum* Diels & Gilg	Regulate Wnt/β-catenin signaling pathway	[143]
Inhibit angiogenesis	Scutellarin	*Scutellaria baicalensis* Georgi	Target ephrinb2	[144]
	Oleanolic acid	*Ligustrum lucidum* W.T.Aiton	Inhibit STAT3 and Hedgehog pathway	[146]
	Celastrol	*Tripterygium wilfordii* Hook. f.	Suppress synthases of NO	[147]
Inhibit proliferation, invasion, migration and other function	*Scutellaria barbata* D.	*Labiatae*	Suppress PI3K/AKT and TGF-β/Smad signaling pathways	[151]
	Berberine	*Coptis chinensis* Franch.	Regulate COX-2/PGE2 Mediated JAK2/ STAT3 Signaling Pathway	[152]

apoptosis, and inhibit proliferation and migration of colorectal cancer [137]. Ginkgolic acid, a phenolic acids isolated from the seed coat of *Ginkgo biloba* L., participates in ROS regulated apoptosis and autophagy [138]. Gambogic acid from *Garcinia hanburyi* Hook.f. causes cell cycle arrest at G1, induces apoptosis, and suppresses colon cancer cell proliferation and migration [139]. Icariin, a flavonol glycoside isolated from *Epimedium brevicornu* Maxim., induces apoptosis via P53 dependent manner and suppresses migration of colorectal cancer [140]. Betulinic Acid, a pentacyclic triterpenes extracted from *Betula mandshurica* (Regel) Nakai, suppresses colorectal cancer migration through mitochondria-mediated apoptotic [141]. Shikonin, a quinones from *Lithospermum erythrorhizon* Siebold & Zucc. targets galectin-1/JNK signaling axis, and induces autophagy and apoptosis [142]. Radix Tetrastigma hemsleyani flavone, extracted from *Tetrastigma hemsleyanum* Diels & Gilg induces cell cycle arrest at G0/G1 phases and causes apoptosis to suppress EMT [143].

5.3. Blocking the angiogenesis

Scutellarin, a flavonoid extracted from *Scutellaria baicalensis* Georgi, as a good inhibitor of angiogenesis, can decrease colon cancer cell extract nutrition from adjacent tissue mucosa, exerting an inhibition metastasis effect via target ephrinb2 [144]. 3, 3′, 4′-trimethylellagic acid, a tannin compound isolated from *Sanguisorba officinalis* L. could also inhibit angiogenesis [145].Oleanolic acid, a pentacyclic triterpenoids isolated from *Ligustrum lucidum* W.T.Aiton, inhibits STAT3 and Hedgehog pathway, and induces angiogenesis suppression [145]. Celastrol, a triterpenes extracted from *Tripterygium wilfordii* Hook. f., plays a role in suppressing synthases of NO and angiogenesis of colorectal cancer [147].

5.4. Suppressing proliferation, migration and invasion of colorectal cancer cells by TCM

Jiedu Sangen Decoction has been used to treat CRC in Zhejiang Hospital of TCM for many years, and experiment has found that it decreases YAP and TAZ of the Hippo signaling pathway, and inhibits EMT and invasion of colorectal cancer. It can also inhibit liver metastasis in a mouse model [148,149].

Ethanol extract of *Scutellaria barbata* D. Don from Labiatae inhibits migration of colorectal cancer. And one compound polysaccharide has been investigated that it can also inhibit liver metastasis induced by TGF-β1 [150,151]. Investigation shows that Berberine can suppress lung metastasis via COX-2/PGE2 mediated JAK2/STAT3 signaling pathway [152].

Investigating research on TCM treatment for colon cancer in recent five years, it is found that Jianpi Jiedu decoction and Jiedu Sangen Decoction, two TCM prescription used in clinic for many years, have good effect on treatment of colorectal cancer. Solasodine has functioned in inhibiting stemness, and the stemness of cancer cells means that cancer cells have the ability of self-proliferation and differentiation. This is one of the main reasons for the unlimited proliferation of cancer cells. The suppression of cancer stemness can also be one of the ways to suppress cancer. Sophoridine, using Network pharmacology to predict the target and verify the predicted, gives a new method in investigating new compound.

6. The advantages of TCM in the treatment of gastric cancer

Gastric cancer is a malignant tumor that originates from gastric mucosal epithelial cells. Gastric cancer has the third highest mortality rate in the world and is more common in men. The causes include chronic irregular diet and overeating, Helicobacter pylori (H. pylori) and Epstein-Barr virus (EBV) infection, long-term diseases and genetic factors. Helicobacter pylori (H. pylori) and Epstein-Barr virus (EBV) infection can cause changes in the intestinal microenvironment and cause gastric cancer [153,154]. The early symptoms of gastric cancer are not obvious, and the only symptoms of upper abdominal discomfort are easily ignored, so the diagnosis of gastric cancer is mostly in the advanced stage [154]. Gastric cancer metastasis includes direct metastasis to the surrounding colon, pancreas, liver, and other organs, blood to other distant organs, peritoneal dissemination, and lymphatic metastasis. Among them, peritoneal metastasis is the most important cause of poor clinical prognosis of gastric cancer [155,156].

According to pathological process of gastric cancer metastasis, it has been reported that gastric cancer metastasis is inhibited by TCM through different mechanisms. This review has summarized the reported effective mechanisms of TCM, such as inhibiting the EMT, promoting apoptosis, inhibiting angiogenesis, inducing cell cycle arrest and inhibiting proliferation, migration, invasion and other function, shown in Table 5.

6.1. Inhibiting EMT of gastric cancer cells by TCM

By analyzing the 39 human derived gastric cancer tumor and adjacent tissue samples, KLF5 and HIF-1α were upregulated in tumor. After treating Crocin, a carotenoid isolated from *Crocus sativus* L. administration, the expression of KLF5 and HIF-1α was inhibited. KLF5 is the target gene of miRNA-320, and miRNA has functioned in inhibiting target gene expression. Detection of gastric cancer cells after Crocin administration revealed that the expression of miRNA-320 was up- regulated and the expression of KLF5 was inhibited. Therefore, miR- 320/KLF5/HIF-1α may be the molecular mechanism of Crocin's treatment of gastric cancer [157]. 28-Hydroxy-3-oxoolean-12-en-29-oic Acid, a triterpene Acid from *Celastrus orbiculatus* Thunb., has functioned in influenced EMT related maker involved in regulating EMT [158]. Daurinoline, a daurinoline isolated from *Euchresta japonica* Regel, can sensitize the gastric cancer cells to Taxol and inhibit EMT [159].

6.2. Blocking the angiogenesis

Xiaotan Sanjie decoction inhibits the angiogenesis of gastric cancer cells and inhibits its metastasis. Jun Shi et al. discovered through

Table 5
The mechanisms of TCM in attenuating gastric cancer.

Function	Compound/single TCM	Origin	Molecular mechanism	
Inhibit EMT	Crocin	*Crocus sativus* L.	Regulate miR-320 / KLF5 / HIF-1α	[157]
	28-Hydroxy-3-oxoolean-12-en-29- oic Acid	*Celastrus orbiculatus* Thunb.	Regulate EMT related maker	[158]
	Daurinoline	*Euchresta japonica* Regel	Inhibit Notch-1	[159]
Induce cell cycle arrest	Berberine	*Coptis chinensis* Franch.	AMPK-HNF4α-WNT5A signaling pathway	[162]
	Curcumin	*Curcuma longa* L.	Increase miR-34a expression	[163]
	Andrographolide	Andrographis paniculata Nees	Activate MMPs	[161]
Induce apoptosis	*Celastrus orbiculatus* Thunb.	Celastraceae	Target maspin and NF-κB/Snail Signaling Pathway	[165, 166]
	Isoliquiritigenin	*Glycyrrhiza uralensis* Fisch.	Suppress PI3K/AKT/mTOR signaling pathway	[167]
	Paeonol	*Paeonia* × *suffruticosa* Andrews	Downregulate MMP-2 and MMP-9	[168]
	Ginkgo Biloba	*Ginkgoaceae*	Regulate ERK/NF-κB/MMP2 signaling cascade	[170]
	Celastrol	*Tripterygium wilfordii* Hook.	Downregulate Biglycancan elevate RIP1/RIP3/MLKL signaling pathway	[171]
Inhibit invasion, migration and other function.	Cantharidin	f. *Mylabris phalerata* Pallas	Suppress PI3K/AKT signaling pathway	[172]
	Matrine	*Sophora flavescens* Aiton	Upregulate AHNAK and downregulate miR-93-5p	[173]

research that Xiaotan Sanjie decoction could achieve this process by inhibiting IL-8-regulated VEGF-VEGFR signaling system [160].

6.3. Causing cell cycle arrest

Andrographolide, a diterpene lactone isolated from *Andrographis paniculata* (Burm.f.) Nees, causes cell cycle arrest at G2/M phase while induces apoptosis and then inhibits migration of gastric cancer [161]. Berberine induces cell cycle arrest in G0/G1 phase and can also suppress the gastric cancer tumor growth in vivo through AMPK-HNF4α-WNT5A signaling pathway [162]. Curcumin can also induce cell cycle arrest at G0/G1 phase through increasing the content of miR-34a expression [163].

6.4. Inducing cell apoptosis

Tengyang Ni et al. found that Huachansu Capsule induced apoptosis of gastric cancer cells through Akt/mTOR pathway, the cycle was arrested, its proliferation was inhibited, and xenograft mouse model tumor growth was inhibited [164].

Celastrus orbiculatus Thunb. extracts from Celastraceae can target the maspin gene and NF-κB/Snail Signaling Pathway induce apoptosis, and inhibit migration and invasion of human gastric adenocarcinoma cells [165,166].

Isoliquiritigenin, a flavonoid isolated from *Glycyrrhiza uralensis* Fisch. suppresses PI3K/AKT/mTOR signaling pathway and is followed with inhibition of apoptosis and autophagy related proteins [167]. Paeonol, a phenols isolated from *Paeonia* × *suffruticosa* Andrews, downregulates MMP2 and MMP9, induces apoptosis, and inhibits metastasis of gastric cancer [168]. Rhein induces gastric cancer SGC-7901 cell apoptosis through mitochondrial dependent manner [169].

6.5. Suppressing proliferation, migration and invasion of gastric cancer cells by TCM

Ginkgo Biloba extract from Ginkgoaceae, suppresses proliferation, invasion and migration ability of gastric cancer cell. Deep mechanism found that it was through ERK/NF-κB/MMP2 signaling cascade. Ginkgo Biloba Extract can inhibit orthotopic tumors of gastric cancer in animals. Measuring the expression of ERK/NF-κB/MMP2 signaling cascade, it is found that it has the same effect on gastric cancer cells [170].

Celastrol, a triterpenes extracted from *Tripterygium wilfordii* Hook. f., downregulates Biglycancan, elevates RIP1/RIP3/MLKL signaling pathway and promotes necroptosis [171]. Cantharidin, a Monoterpenes isolated from *Mylabris phalerata* Pallas, inhibits migration through suppressing PI3K/AKT signaling pathway [172]. Matrine inhibits migration of gastric cancer by upregulating AHNAK and downregulating miR-93-5p [173].

7. The advantages of TCM in the treatment of other cancer metastasis

7.1. Ovarian cancer

Compound Fuling Granule, Shanming Ruan et al., through metabolic enrichment and pathway enrichment, was found to exert its role by malfunctioning mitochondria and regulating the metabolism of lactose and fatty acids. Fangfang Tao et al. found that it could inhibit ovarian cancer metastasis by regulating cell cycle, apoptosis and aging and inhibiting the expression of EMT-related protein maker [174,175]. Aqueous Extract of Paris polyphylla (AEPP) have functioned in inducing apoptosis and through suppressing (PGC)-1alpha, it can induce Mitochondrial Fusion thus inhibiting EMT [176].

Dihydroartemisinin, a sesquiterpene lactone extracted from *Artemisia annua* L., through suppressing the hedgehog signaling pathway, functions in inducing apoptosis and inhibiting proliferation, invasion and migration of ovarian cancer cells [177]. Isoliquiritigenin inhibits EMT

related Transcription Factor and inhibits metastasis of ovarian cancer [178]. Oridonin, a diterpenoid isolated from *Rabdosia rubescens* (Hemsl.) H.Hara. has functioned in inducing apoptosis and causing cell cycle attest. For inhibiting metastasis, it functions through mTOR pathway [179]. Through RNA sequencing and KEGG analysis, Resibufogenin from *Bufo bufo gargarizans* Cantor can induce apoptosis and inhibit proliferation, migration and invasion through suppressing PI3K/AKT and actin cytoskeleton pathways [180].

7.2. Squamous cancer

Aidi injection has functioned in inhibiting EMT of esophageal squamous cancer cell and HUVECs angiogenesis [181]. Qigesan suppresses Gas6/Axl and NF-κB signal pathway and regulates squamous cancer cell motility [182].

Garcinol suppresses expression of TGF-β1 pathway and p300 to inhibit EMT of squamous cancer cell [183]. P-Hydroxylcinnamaldehyde induces cell cycle arrest in G0/G1 phase, influencing the cAMP-RhoA-MAPK signaling pathway [184].

7.3. Melanoma cancer

Piceatannol induces apoptosis through promoting expression of miR- 181a [185]. Atractylenolide I, a sesquiterpene isolated from *Atractylodes macrocephala* Koidz. induces apoptosis and inhibits JAK2/STAT3 pathway [186]. Paeonol, a phenols isolated from *Paeonia* × *suffruticosa* Andrews inhibits metastatic potential through NF-κB and STAT3 signal pathways [187]. Licochalcone D, a flavone Glycyrrhiza inflate induces apoptosis, and inhibits proliferation and migration of melanoma cancer [188]. Holothurian glycosaminoglycan can inhibit metastasis of melanoma cancer via suppress P-selectin and β3 integrins and FAK at protein levels [189]. Ethanol extract of *Alocasia cucullata* (Lour.) G.Don from Araceae. inhibits migration of melanoma cancer through regulate the PI3K/AKT signaling pathway [190]. Cryptotanshinone, a Diterpene quinones isolated from *Salvia miltiorrhiza* Bunge has function in inducing apoptosis and causing cell cycle arrest at G2/M phase [191]. Scutellarin a flavonoid extracted from *Scutellaria baicalensis* Georgi, suppresses EMT and angiogenesis via PI3K/Akt/mTOR signaling pathway [192]. Apigenin inhibits melanoma metastasis through STAT3 signaling pathway [193]. Gambogic Acid inhibits migration of melanoma cancer through regulating miR-199a-3p/ZEB1 Signal [194].

7.4. Pancreatic cancer

Qingyihuaji formula regulates the lncRNA AB209630/miR-373/ EphB2-NANOG signals, exerting good effect on reversing gemcitabine resistant pancreatic cancer [195]. Dihydrosanguinarine, an alkaloid isolated from *Chelidoniummajus* L., causes cell cycle arrest in G0/G1 and G2/M phase, and induces apoptosis through Ras/Raf/Mek/Erk signaling pathway [196]. Matrine, through regulating ROS/NF-κB/MMPs pathway, inhibits EMT of pancreatic cells [197]. Toosendanin, a triterpenoid isolated from *Melia azedarach* L., inhibits EMT through regulating Akt/mTOR signal [198]. Astragalus polysaccharide combining with apatinib, gets good effect on treatment of pancreatic cancer's proliferation, invasiveness, and apoptosis [199]. Baicalein, a flavonoid isolated from *Scutellaria baicalensis* Georgi, suppresses the expression of Survivin and tumor growth of pancreatic cancer [200], shown in Table 6.

8. Discussion and future perspectives

Tumor metastasis is an important marker of tumor deterioration. A large number of studies have shown that the five-year survival rate of tumors after metastasis will be severely reduced. Epithelial-mesenchymal transition (EMT) and tumor angiogenesis play important roles in tumor metastasis. The tumor first undergoes angiogenesis to accumulate energy in the primary location, and then undergoes the EMT process from epithelial cells to mesenchymal cells. After the tumor cells are transformed into mesenchymal cells, they escape the recognition of the immune system and leave the original implantation site to enter the blood vessels or lymph tube, entering into other metastases as the blood circulates. Corresponding protein expression in tumor cells during angiogenesis and EMT will change accordingly, such as the proteins of Vimentin, N-Cad, E-Cad and vascular endothelial growth factor (VEGF) etc. Changes that affect the expression of such proteins can also affect the process of tumor cell metastasis [5]. (Fig. 2) Mitochondria plays an important role in the process of tumor cell metastasis. Mitochondria can provide energy for cell metastasis in the cell, while inhibiting mitochondrial function can inhibit tumor metastasis [7]. This article mostly focuses on autophagy and apoptosis in tumor cells during metastasis, EMT of cancer cells and tumor angiogenesis. In addition, the tumor microenvironment also has a great impact on the tumor. In the tumor microenvironment, M1 type macrophages are transformed into M2 type macrophages under the influence of tumor cells to promote tumor growth. Tumor cells express PD-L1 and bind to PD1 on the surface of immune system T cells, so that T cells recognize tumor cells as normal cells, and immune escape occurs [201,202].

As a treasure of China, TCM has the characteristics of low toxic and side effects, less damage to the body with multiple targets. TCM prescription has wonderful effects on the treatment of tumors, but its mechanism for treating cancer is difficult to elucidate. Many TCM prescriptions (Table 7) have been clarified to have good effect on anti-cancer treatment clinically such as Fuzheng Kang-Ai decoction, Jinfu'an Decoction and YangZheng XiaoJi used for treating lung cancer, Jiedu Recipe for hepatic carcinoma, Jianpi Jiedu decoction and Jiedu Sangen Decoction for colorectal cancer. The clarification of the effective ingredients in the prescription and the specific molecular targeting mechanism of each ingredient require a complex process. In the past five years, the research on the anti-cancer mechanism of TCM prescription is mostly manifested in the inhibitory effect on the proliferation, migration and invasion of tumor cells during tumorigenesis. But no clarification of its

effective ingredients and the anti-cancer molecular mechanism of its ingredients have been elucidated. TCM prescription has many active ingredients, and every ingredient has the characteristics of multiple targets in the body, so to clarify its specific mechanism of action on cancer requires a lot of work. The representative component of Compound Kushen Injection in Chinese patent medicine has multiple targets predicted by network pharmacology, including inhibition of tumor proliferation, invasion, migration, angiogenesis, etc. and Compound Kushen Injection can be used for a variety of cancers including colorectal cancer, breast cancer and liver cancer [26,110]. Research of the anticancer effect of a certain monomer compound in TCM has made considerable progress in recent years, of which are representatives like Apigenin, matrine, Resveratrol, Rhein, Tetrandrine, Berberine, Timosaponin AIII and Shikonin [203–210]. Among the monomer compounds in TCM, Berberine,

Table 6
The mechanisms of TCM in alleviating other cancer.

Cancer type	Compound/single TCM	Origin	Function	
Ovarian cancer	Aqueous Extract of Paris polyphylla (AEPP)	*Liliaceae Juss.*	Suppress (PGC)-1alpha and induce Mitochondrial Fusion	[176]
	Dihydroartemisinin	*Artemisia annua* L.	Suppress the hedgehog signaling pathway	[177]
	Isoliquiritigenin	*Glycyrrhiza uralensis* Fisch.	Suppress EMT	[178]
	Oridonin	*Rabdosia rubescens* (Hemsl.) H.Hara.	Cause cell cycle arrest Inhibit mTOR pathway	[179]
	Resibufogenin	*Bufo bufo gargarizans* Cantor	Suppress PI3K/AKT and actin cytoskeleton pathways	[180]
Squamous cancer	Garcinol	*Garcinia yunnanensis* Hu	Suppress TGF-β1 pathway and p300	[183]
	P-Hydroxylcinnamaldehyde	*Momordica cochinchinensis* (Lour.) Spreng.	Influence the cAMP-RhoA-MAPK signaling pathway.	[184]
	Piceatannol	*Veratrum grandiflorum* (Maxim. ex Miq.) O.Loes.	promote expression of miR-181a	[185]
	Atractylenolide I	*Atractylodes macrocephala* Koidz.	Inhibit JAK2/STAT3 pathway	[186]
	Licochalcone D	*Glycyrrhiza inflata* Batalin	Inhibit proliferation, induce apoptosis through mitochondrial pathway	[188]
Melanoma cancer	Holothurian glycosaminoglycan	*Holothuria insignis*	Suppress P-selectin and β3 integrins and FAK at protein levels	[189]
	Alocasia cucullata (Lour.) G.Don	*Araceae Juss.*	Regulate the PI3K/AKT signaling pathway	[190]
	Cryptotanshinone	*Salvia miltiorrhiza* Bunge	Induce apoptosis; Cause cell cycle arrest in G2/M phase	[191]
	Scutellarin	*Scutellaria baicalensis* Georgi	Regulate PI3K/Akt/mTOR signaling pathway	[192]
	Apigenin	*Plantago asiatica* L. or *Plantago depressa* Willd.	Regulate STAT3 signaling pathway.	[193]
	Gambogic Acid	*Garcinia hanburyi* Hook.f.	Regulate miR-199a-3p/ZEB1 Signal	[194]
Pancreatic cancer	Dihydrosanguinarine	*Chelidonium majus* L.	Regulate mut-p53/WT-p53 and Ras/Raf/Mek/Erk pathway	[196]
	Matrine	*Sophora flavescens*		[197]
	Toosendanin	Aiton *Melia azedarach* L.	Regulate ROS/NF-κB/MMPs pathway	[198]
	Astragalus polysaccharide	*Astragalus propinquus* Schischkin	Regulate Akt/mTOR signal	[199]
	Baicalein	*Scutellaria baicalensis* Georgi	Downregulate of p-AKT, p-ERK, and MMP-9 expression Suppress the expression of Survivin	[200]

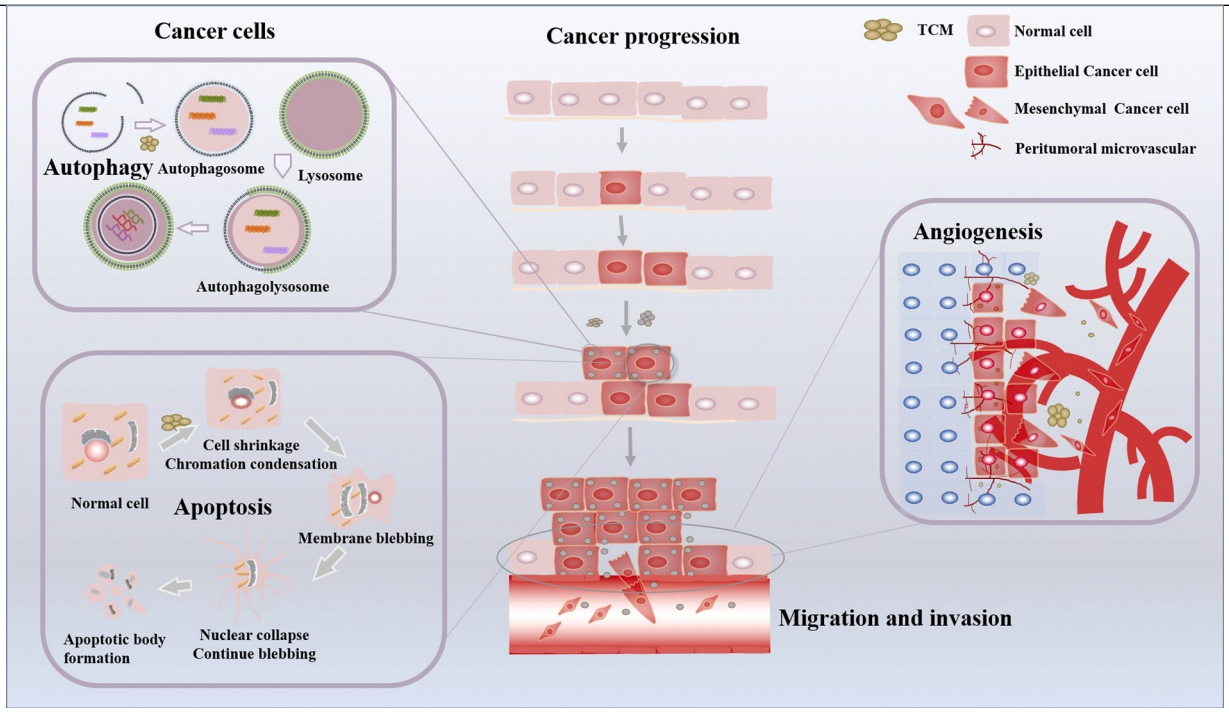

Fig. 2. Mechanism of TCM in the therapy of cancer against metastasis With the characteristic of unlimited proliferation, cancer cells have lost their original cell functions and are more likely to migrate. With the circulation of blood, they cause cancer metastasis. Chinese medicine treatment can inhibit cancer metastasis through various mechanisms and play an anti-cancer effect, including 1. inhibiting the mutation of tumor cells and the EMT of tumor cells;2. promoting the formation of autophagosomes and the autophagy of cancer cells;3. stimulating nuclear shrinkage and lysis of cancer cells and promoting apoptosis of cancer cells;4. inhibiting angiogenesis, reducing the distribution of blood vessels around tumor tissue, and suppressing the growth of tumor cells.

Resveratrol, Onionin A, Genistein and Curcumin also have related studies in tumor microenvironment and immune regulation [211–217]. For combination with clinical

Table 7
TCM prescription and patent medicine for cancer treatment.

Cancer type	Chinese patent medicine/ prescription	Compose	Mechanism	
Breast cancer	Qingdu granule	*Bupleurum chinense* DC.; *Citrus reticulata* Blanco; *Curcuma wenyujin* Y. H. Chen et C. Ling; *Sophora japonica* L.; *Paeonia suffruticosa* Andr.; *Arnebia euchroma* (Royle) Johnst.; *Prunella vulgaris* L.; *Salvia miltiorrhiza* Bge.; *Curcuma phaeocaulis* Val.; *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao; *Glycyrrhiza uralensis* Fisch.; *Sophora flavescens* Aiton; *Polyporus umbellatus* (Pers.) Fries;	Inhibit angiogenesis Inhibiting NFAT signaling pathway	[19]
	Compound Kushen injection		Delay the formation of filopodia; Inhibit the expansion of lamellipodia,; Change the cytoskeleton proteins;	[26]
	Chinese medicine formula T33	*Radix Kansui*; *Paeonia lactiflora*; *Pinelliae Rhizoma Praeparatum*; *Glycyrrhizae Radix et Rhizoma*; *Rheum rhabarbarum;*	Induce autophagy	[39]
	Bu-fei Decoction	*Codonopsis pilosula* (Franch.) Nannf.; *Astragalus propinquus* Schischkin; *Schisandra chinensis* (Turcz.) Baill.; *Rehmannia glutinosa* (Gaertn.) DC.; *Aster tataricus* L.f.; *Morus alba* L.;	Inhibit EMT through suppress TGF-β1	[60]
	Fuzheng Kang-Ai decoction	*Pseudostellaria heterophylla* (Miq.) Pax; *Atractylodes macrocephala* Koidz.; *Astragalus propinquus* Schischkin; *Oldenlandia diffusa* (Willd.) Roxb.; *Solanum nigrum* L.; *Rubia yunnanensis* Diels; *Cremastra appendiculata* (D. Don) Makino; *Coix lacryma-jobi var. ma-yuen* (Rom.Caill.) Stapf; *Akebia quinata* (Houtt.) Decne.; *Rubus parviflolius* L.;	Inhibit EMT through regulate STAT3 / MMP9 pathway	[61]
	Bushenshugan Formula	C*urcuma phaeocaulis* Valeton; *Glycyrrhiza uralensis* Fisch.; *Bupleurum marginatum* Wall. ex DC.; *Schisandra chinensis* (Turcz.) Baill.; *Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav.; *Paeonia veitchii* Lynch; *Lycium barbarum* L.; *Cuscuta chinensis* Lam.; *Plantago depressa* Willd.; *Rubus idaeus* L.; *Astragalus propinquus* Schischkin; *Epimedium brevicornu* Maxim.; *Houttuynia cordata* Thunb.; *Trichosanthes kirilowii* Maxim.; *Allium fistulosum* L.; *Prunella vulgaris* L.; *Ligustrum lucidum* W.T.Aiton; *Polyporus umbellatus* (Pers.) Fries; *Gentiana scabra* Bunge;	Regulate PI3K/AKT/NF-κB pathway	[62]
Lung cancer	Huaier Granule	*Trametes robiniophila murr*	Inhibit the proliferation and metastasis of lung cancer cells through down-regulation of MTDH, JAK2/STAT3 and MAPK signaling pathways	[67]
	Xiaoai Jiedu Recipe	*Oldenlandia diffusa* (Willd.) Roxb.; *Cremastra appendiculata* (D.Don) Makino; Bombyx batryticatus; *Scolopendra subspinipes mutilaus* L. Koch;	Induce apoptosis through activate P38 MAPK pathway	[68]
	Jinfu'an Decoction	*Akebia trifoliata* (Thunb.) Koidz.; *Pseudostellaria heterophylla* (Miq.) Pax; *Ophiopogon japonicus* (Thunb.) Ker Gawl.; *Pseudostellaria heterophylla* (Miq.) Pax; *Cremastra appendiculata* (D.Don) Makino; *Coix lacryma-jobi* L.; *Salvia miltiorrhiza* Bunge; *Gekko japonicas*	Down-regulates p120ctn; Up-regulates the expression of Kaiso;	[76]
	YangZheng XiaoJi	Dumeril et Bibron; *Prunus persica* (L.) Batsch; *Phragmites communis* Trin; *Fritillaria thunbergii* Miq.; *Pinellia ternata* (Thunb.) Makino; *Arisaema heterophyllum* Blume; *Panax ginseng* C.A. Mey.; *Astragalus propinquus* Schischkin; *Ligustrum lucidum* W.T.Aiton; *Curcuma phaeocaulis* Valeton; *Ganoderma Lucidum* Karst; *Gynostemma pentaphyllum* (Thunb.) Makino; *Atractylodes macrocephala* Koidz; *Scutellaria barbata* D.Don; *Oldenlandia diffusa* (willd.) Roxb; *Poria cocos* (Schw.) Wolf; *Duchesnea indica* (Jacks.) Focke; *Solanum lyratum* Thunb.; *Artemisia scoparia* Waldst. & Kitam.; *Cynanchum paniculatum* (Bunge) Kitag. ex H.Hara; *Steleophaga* Plancyi	Inhibit HGF and its receptor, cMET	[77]
Hepatic carcinoma	Jiedu Recipe	(Boleny); *Gallusgallusdomesticus* Brisson; *Actinidia valvata* Dunn; *Salvia chinensis* Benth.; *Cremastra appendiculata* (D.Don) Makino; *Gallusgallusdomesticus* Brisson;	Regulating the Smad-related pathway and MAPKs and Akt-related pathway	[86]
	Yanggan Jiedu Sanjie	*Ligustrum lucidum* W.T.Aiton; *Scutellaria barbata* D.Don; *Solanum nigrum* L.; *Duchesnea indica* (Andr.) Focke; *Curcuma wenyujin* Y.H. Chen et C. Ling; *Euphorbia helioscopia* L.; *Ranunculus ternatus* Thunb.; *Polygonum cuspidatum* Sieb. et Zucc.	Inhibit TGF-β1-induced EMT	[87]
	Qizhu decoction	*Phyllanthus urinaria* L.; *Polygonum cuspidatum* Sieb. et Zucc.; *Oldenlandia diffusa* (Willd.) Roxb.; *Paeonia lactiflora* Pall.; *Paeonia veitchii* Lynch;	Inhibit EMT, induce cell cycle arrest, induce apoptosis via NF-κB signaling	[112]
Colorectal cancer	Zuo Jin Wan	*Smilax china* L.; *Salvia miltiorrhiza* Bunge; *Coptis chinensis* Franch.; *Euodia rutaecarpa* (Juss.)Benth.;	Inactivated Wnt/β-catenin signaling	[129]
	Jianpi Jiedu	*Astragalus propinquus* Schischkin; *Panax quinquefolius* L.;	Regulate mTOR/HIF-1α/VEGF pathway	[127]

	decoction	*Atractylodes macrocephala* Koidz.; *Poria cocos*(Schw.)Wolf; *Coix lacryma-jobi var. ma- yuen* (Rom.Caill.) Stapf; *Smilax china* L.; *Oldenlandia diffusa* (Willd.) Roxb.; *Scutellaria barbata* D.Don; *Paris polyphylla* Sm.; *Actinidia argut*; *Glycyrrhiza uralensis* Fisch;		
	Jiedu Sangen Decoction	*Actinidia arguta* (Siebold & Zucc.) Planch. ex Miq.; *Adina rubella* Hance; *Polygonum cuspidatum* Siebold & Zucc.	Decrease YAP and TAZ	[148]
Gastric cancer	Xiaotan Sanjie decoction	*Arisaema heterophyllum* Blume; *Pinellia ternata* (Thunb.) Makino; *Buthus martensii* Karsch□*Scolopendra subspinipes mutilans* L.Koch; *Cremastra appendiculata* (D. Don) Makino; *Gallusgallusdomesticus* Brisson; *Citrus reticulata* Blanco; *Poria cocos*(Schw.)Wolf; *Glycyrrhiza uralensis* Fisch.;	Inhibiting IL-8-regulated VEGF-VEGFR signaling system	[160]
Squamous cancer	Qigesan	*Curcuma wenyujin* Y.H. Chen et C. Ling; *Adenophora tetraphylla*(Thunb.) Fisch.; *Salvia miltiorrhiza* Bunge; *Fritillaria thunbergii* Miq.; *Poria cocos* (Schw.)Wolf; *Amomum villosum* Lour.; *Nelumbo nucifera* Gaertn.; *Pinellia ternata* (Thunb.) Makino; *Triticum aestivum* L.; *Asparagus cochinchinensis* (Lour.) Merr.; *Dioscorea oppositifolia* L.;	Inhibiting Gas6/Axl and NF-κB expression	[182]

chemotherapy drugs, TCM has function in many ways like prolonging the patients survival time, reducing the dose of chemotherapy drugs, reversing drug resistence, alleviating patients adverse reaction and so on. Related research like artemisinin combines with vinorelbine (NVB), curcumin enhances cisplatin sensitivity, cryptotanshinone reverses cisplatin resistance, triptolide combined with cisplatin result in enhancing apoptosis, and Ginsenoside Rg3 enhances the efficacy of Paclitaxel [218–222].

This article mostly focuses on the research on breast cancer, lung cancer, hepatic cancer, colorectal cancer and gastric cancer metastasis in the past five years. The combined application of TCM and clinical medicine can often achieve unexpected results. The combined application of TCM with clinical chemotherapy drugs can enhance the efficacy of clinical chemotherapy drugs, reduce their side effects, and improve the patient's survival time and quality of life. TCM prescriptions, Chinese patent medicines, single Chinese medicines and TCM monomer compounds are often not unilateral for the treatment of cancer. The inhibitory effect of TCM on metastasis often manifests in inhibiting the expression of EMT-related proteins, thereby inhibiting EMT, inhibiting the expression of angiogenesis-related proteins, inhibiting angiogenesis, regulating cell autophagy, regulating apoptosis, and regulating mitochondrial function. TCM plays an important role in the treatment of cancer. Compared with the progress of clinical chemotherapeutics, the research progress of TCM is slower, and the research on the mechanism of Chinese medicine compound on cancer is still rare. The theoretical treatment of TCM emphasizes the use of compound. Therefore, there will be more related researches on the treatment of cancer focusing TCM prescription.

Author contribution

These authors have contributed equally to this work

Declaration of Competing Interest

No potential conflicts of interest are disclosed.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biopha.2020.111044.

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